PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 804 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08077	International filing date *(day/month/year)* 23.07.2003	Priority date *(day/month/year)* 23.07.2003
International Patent Classification (IPC) or both national classification and IPC A61K31/553		
Applicant CREABILIS THERAPEUTICS s.r.l.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.07.2004	20.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Albayrak, T Telephone No. +49 89 2399-7549

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08077

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-5 as originally filed

Claims, Numbers

1-7 filed with telefax on 15.11.2004

Drawings, Sheets

1/2, 2/2 filed with telefax on 15.11.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4,7
	No:	Claims	5-6
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item V

1. Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

   D1: WO 97 49406 A (AIMONE LISA D ;CEPHALON INC (US); ENGBER THOMAS M (US); HAUN FORRE) 31 December 1997 (1997-12-31)
   D2: WO 96 11933 A (CEPHALON INC) 25 April 1996 (1996-04-25)
   D3: AKINAGA: 'Antitumor effect of KT6124, a novel derivative of protein kinase inhibitor k-252a, and its mechanism of action' CANCER CHEMOTHERAPY AND PHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 29, no. 4, 1992, pages 266-272, XP002104872 ISSN: 0344-5704

2. **Novelty**

   Independent claim 1 is directed to the use of K252 or several derivatives, among them such "obtained by chemical synthesis aimed to reduce the systemic absorption of the product by means of spacers associated to proteins **or other physiologically inactive large molecules**".
   D1 discloses a derivative of K252 with a side chain that must be regarded as a "spacer associated to... physiologically inactive large molecules". Since the specification "large" does not lead to any meaningful identification of compounds the derivative of D2 must be regarded to fall within the scope of the definition of D1.

   D1 discloses powders, drops and transdermal patches as possible ways of administration. Thus, the subject-matter of claims 5 and 6 is not novel (Art. 33(2) PCT).

3. **Inventive merits**

- Claim 7 is obvious to the skilled person in the light of D1 or D2. The document discloses compounds structurally highly similar to K252a and K252b and disclose the topical administration route.
  The skilled person would be prompted to prepare a topical pharmaceutical composition with K252a since the document teaches the use of K252a for treating psoriasis. Claim 7 lacks an inventive step (Art. 33(3) PCT).

- Claims 1-4 lack an inventive step.

Claim 1 is directed to the use of K252 or several derivatives of K252 for treating disorders characterised by hyperproliferation of keratinocytes.

The use of K252-derivatives for treating such diseases are already known from D2 (psoriasis), D1 (psoriasis) and D3 (skin melanoma).
Thus, the differentiating feature between claim 1 and D1-D3 is the route of administration (topical).
However, D1 already teaches the use of several different administration routes among them topical administration via powders or patches.
In the light of this teaching no surprising/unexpected effect can be regarded from claims 1-4.
Claims 1-4 lack an inventive step (Art. 33(3) PCT).

CLAIMS

1. Use of the alkaloid K252 or of their physiologically equivalent derivatives selected from esters, amides, salts, N-alkylated or N-acylated derivatives or derivatives obtained by chemical synthesis aimed to reduce the systemic absorption of the product by means of spacers associated to proteins or other physiologically inactive large molecules, for the preparation of topical drugs for the treatment of disorders characterised by hyperproliferation of keratinocytes.

2. Use as claimed in claim 1, wherein the active ingredient is K252a or K252b.

3. Use as claimed in claim 1or 2, wherein the disorders are psoriasis and skin tumours.

4. Use as claimed in claim 1, 2 or 3 for the preparation of a medicament for use in combination with PUVA treatment or photodynamic treatment.

5. Topical pharmaceutical compositions containing an alkaloid K252 as defined in claim 1 as active ingredient, in admixture with suitable vehicles and excipients.

6. Compositions as claimed in claim 4 in the form of ointments, gels, lotions, powders and medicated plasters.

7. Compositions as claimed in claims 5 or 6 wherein the active ingredient is K252a or K252b.

Figure 1. Exposure of human keratinocytes to K-252a for 1 hour: effects on proliferation.

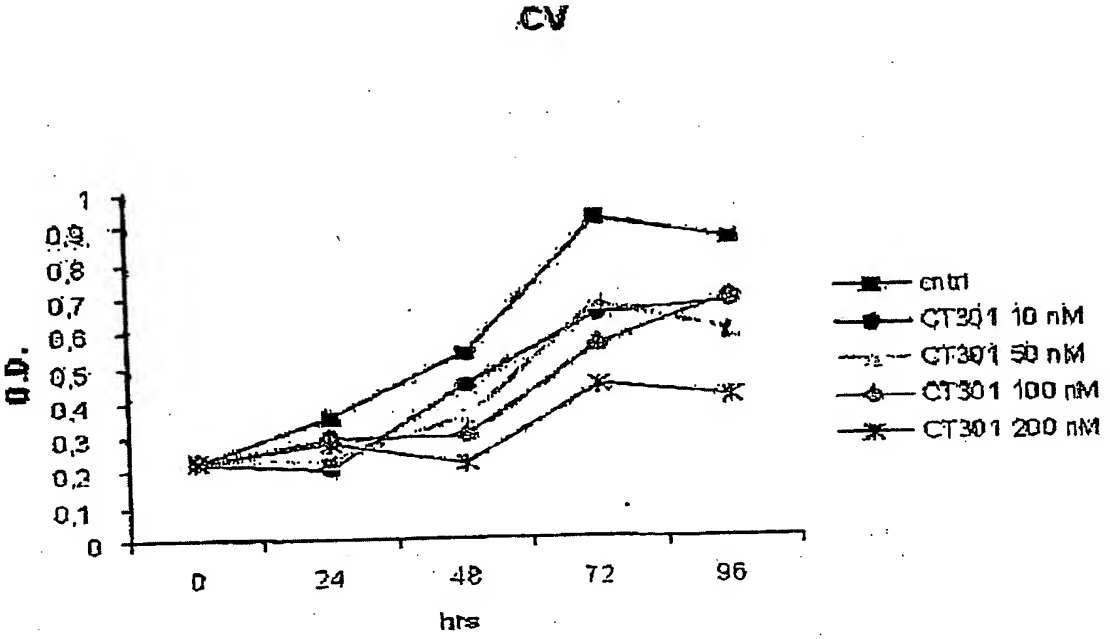

Figure 2. Exposure of human keratinocytes to K-252a for 96 hours: effects on proliferation.